Syndrome of Diabetes Mellitus

Jeannie A. Baquero
Endocrinology Department

Introduction

- 5% of the general population are diagnosed with diabetes
- Diabetes is a significant co-morbid player in other disease processes
- Majority of patients with diabetes are managed by primary care providers.

Subtypes

- Insulin Dependent (Type 1 Diabetes)
  - Lack of insulin production due to pancreatic islet cell dysfunction
  - Prone to ketoacidosis
- Non-insulin dependent (Type 2 Diabetes)
  - A disorder marked by a combination of insulin resistance and a defect insulin secretion

Subtypes Cont.

- Gestational Diabetes
  - a potential prediabetic state recognized during pregnancy
- Secondary Diabetes
  - Pancreatic disease causing insulinopenia
    - Chronic pancreatitis
    - Pancreatectomy
    - Cystic fibrosis
    - Hemochromatosis

Secondary Diabetes

- Endocrinopathies associated with hyperglycemia
  - Increase in counter-regulatory hormones
- Drug or chemical induced
- Genetic defects of beta-cell function or insulin action

Criteria for the Diagnosis of DM

- Symptoms of diabetes mellitus plus a casual plasma glucose concentration of >/= 200mg/dL. Symptoms include:
  - Polyuria
  - Polydipsia
  - Polyphagia
  - Unexplained weight loss

Diagnosis Cont.

- Fasting plasma glucose >/=126mg/dL. Fasting is defined as 8hours or more without caloric intake
- Two-hour plasma glucose >/= 200mg/dL during performance of an oral OGTT. The OGTT should be performed by WHO criteria that include a glucose load containing 75 g of glucose in water

Criteria

- Normoglycemia
  - FPG < 110 mg/dL
  - 2 hr GTT < 140 mg/dL
- IGT
  - FPG >/= 110 and < 126 mg/dL
  - 2 hr GTT >/= 140 and < 200 mg/dL
- Diabetes Mellitus
  - FPG >/= 126 mg/dL,or 2 hr GTT >/= 200
  - symptoms + random plasma glucose >/= 200

Screening for Diabetes

- Age 45 yr and older, if normal results are obtained, screening should be repeated at 3 year intervals
- Younger individuals, or more frequent screening, in the following:
  - Obese Body Mass Index (BMI>/=27 kg/m2 or >/= 120% of desirable body weight
  - Individuals with first degree relatives
  - Members of high-risk ethnic population
  - Have delivered a baby weighing >9 Ibs or diagnosed with gestational diabetes
  - Hypertensive
  - History of impaired glucose tolerance
  - dyslipidemia
  - HDL cholesterol </=35 mg/dL, Triglycerides >/= 250 mg/dL

Etiology of Type I Diabetes

- Susceptibility probably involves more than one gene
- Overall risk of developing diabetes when they have a first degree relative is 5-10%
- A major influence is exerted by MHC
  - 95% of patients with type 1 diabetes have HLA expressions of DR3 and/or DR4
- Environmental triggers (probably viral)

Etiology Cont.

- Antibodies to beta and other cell types, insulin,glutamic acid decarboxylase.
  - Antibodies to GAD appear to be predictive of subsequent diabetes

Presenting Complaints

- Type 1 diabetes
  - Abrupt onset of:
    - Polyuria/polydipsia/polyphagia
    - Weight loss
    - fatigue
  - Usually relatively thin
  - Peak age on onset 11-13 years (usually before age 20)

Etiology of Type 2 DM

- Interaction of genetic and environmental factors that impair insulin secretion and produce insulin resistance
- Impaired glucose uptake by skeletal muscle
- Increased in hepatic gluconeogenesis
- Apparent familial relationship, but no specific gene identified except in MODY

Presenting Complaints

- Type 2 DM
  - Insidious onset of:
    - Polyuria/polydipsia
    - Weight loss
    - weakness/fatigue
    - dizziness,headache,blurred vision
  - Often asymptomatic
  - Can initially present with end organ injury
  - Usually obese
  - Typical age >40

Management

- Diabetic education
  - teaching on disease, complications, finger sticks, insulin injection, urine dipsticks
- Diabetic diet
  - reduced calories
  - 10-15% protein, 50-55% complex CHO, 30-35% fat
  - Dietetic referral

Sulfonylurea

- Mechanism of action:
  - High affinity sulfonylurea receptors found on beta cells. Linked to ATP-ase sensitive K ion channel. Following binding, voltage dependent Ca channels open in response to depolarization and allow influx of Ca. Ca binds to Calmodulin which activates kinases that cause exocytosis of Insulin containing secretory granules.
  - Beta cells sense glucose more efficiently, producing more insulin
  - Suppress hepatic gluconeogensis
  - Decrease glucagon levels

Sulfonylureas Cont.

- First-generation agents:
  - Tolazamide, Tolbutamide
    - metabolized by the liver
- Second-generation agents:
  - Glyburide (Micronase, Diabeta)
    - metabolized by the liver and kidney
    - hypoglycemia 2 x more common as Glypizide
    - 5, 10mg tabs. Max dose 10mg BID. Duration of action 18-24 hrs.

Sulfonylureas Cont.

- Glipizide (Glucotrol)
  - metabolized by liver and kidney, less accumulation with renal failure
  - 5,10mg tabs. Max dose 20mg bid. Duration of action 16-24hrs.
  - Glucotrol XL osmotic delivery system. 5,10mg tabs. Max dose 10mg QD
- Glimepiride(Amaryl)
  - Indicated for use with insulin
  - 1,2,4 mg tabs. Qd dosing. Max dose 8mg

Meglitinide

- Repaglinide (Prandin)
  - rapidly absorbed and excreted primarily be the kidney.
  - Plasma 1/2 life less than 1 hr
  - Dosed more frequently
  - decreased episodes of severe hypoglycemia

Efficacy of oral hypoglycemics

- Patients with highest likelihood of response to oral agents:
  - >40 yrs
  - wt >110-160% of IBW
  - no previous use of insulin, or <40U QD
  - fasting blood glucose <180mg/dL

Adverse Effects of oral hypoglcemics

- Dermatologic (0.1%)
  - rashes, pruritis, erythema multiforme, exfoliative dermatitis.
- Hematologic (0.1%)
  - hemolytic anemia, marrow aplasia
- Gastrointestinal (1-3%)
  - nausea,vomiting, dyspepsia, abn LFT’s
- Hypoglycemia (20%/yr)
  - use of sulfonamide antibiotics, coumadin, ASA, allopurinol potentiates action

Biguanides

- Antihyperglycemic agent since it does increase insulin secretion
- Mechanism of action: causes reduced intestinal absorption of glucose, inhibition of hepatic gluconeogenesis, enhance glucose uptake and utilization in peripheral tissues.
  - Translocation of GLUT 4, GLUT 1 to membrane of skeletal muscle and adipocytes.
- Decrease VLLDL, LDL
- 500mg, 850mgtabs, given TID. Max dose 2500 mg

Adverse effects

- Anorexia, nausea, diarrhea, abdominal discomfort (5-10%)
- Lactic acidosis-very rare, usually occurs in overdoses and in patients with contraindications.
- Contraindications: renal insufficiency, pregnancy, alcoholism, abnormal liver function,renal insufficiency

Thiazolidine derivatives

- Mechanism of action:
  - potentiates insulin sensitivity
  - regulates insulin sensitive genes which control metabolism.
  - Decreases hepatic glucose production
- Troglitazone (Rezulin) - 200, 400mg QD. Max dose 600mg.

Thiazolidine derivatives

- Side effects:
  - Transaminitis 2% of patients, reversible with discontinuation. Recommend monthly LFT's Q month for 6 months f/b Q 2 months for 1 yr
  - Discontinue if >3x nml

Acarbose (precose)

- Intestinal Alpha-glucosidase inhibitor
  - delays intestinal absorption of CHO
- Dose: 25mg QD taken with first bite of meal. Advance to max dose of 100 mg TID (wt>132lbs) or 50mg TID (wt<132lbs)
- Side effects: GI upset, diarrhea and flatulence. Does not cause hypoglycemia in fasting states.